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DEPARTMENT OF HEALTH AND HUMAN SERVICE

Public Health Service

Food and Drug Administration
Kansas City District
Southwest Region
11630 West 80th Street
Lenexa, Kansas 66214-3340

Telephone: (913) 752-2100

October 20, 2004

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
Ref. KAN 2005-01

Mr. George Heidgerken
President and COO
Boehringer Ingelheim Vetmedica, Inc.
2621 N. Belt Highway
St. Joseph, MO 64506

Dear Mr. Heidgerken:

On July 19-29, 2004, Food and Drug Administration (FDA) Investigators performed an inspection of your veterinary pharmaceutical manufacturing operations located in Elwood, KS and St. Joseph, MO. This inspection revealed serious deviations from the current Good Manufacturing Practice (cGMP) regulations, Title 21, Code of Federal Regulations, Parts 210 and 211 (21 CFR 210 and 211). These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). Section 501(a)(2)(B) of the Act requires that the methods used in, or the facilities or controls used for, the manufacture, processing, packing, and holding of drugs conform with cGMP to assure that such drugs meet the requirements of the Act as to safety, and have the identity and strength, and meet the quality and purity characteristics, which they purport or are represented to possess.

The following are examples of the significant deficiencies regarding your firm's Quality System that were cited by our investigators:

Your firm has failed to have adequate sampling and testing to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product as required by 21 CFR 211.110. Specifically, review of the process validation for Oxytetracycline HCl bolus revealed:

- At least three validation runs were performed over a three year period of time using Validation Protocols PQPS-035, approved 4/14/2000; PQPS-035-01, approved 9/19/2000; and PQPS-035-01 SUPPLEMENT, approved 5/28/02. As documented, none provide assurance that a comprehensive study was performed.

- Your firm failed to adequately record process details, including sample size and method of collection, to demonstrate Oxytetracycline HCl was tested in accordance with the validation protocol and approved methods.
- Your documentation does not substantiate rigorous in-process testing was conducted to demonstrate the effectiveness and reproducibility of the process. The sample size used for testing is not always statistically significant.
- The in-process granulation and hopper depletion sample test results fell outside the NADA and validation protocol predefined specification of [redacted]. Blend uniformity has not been adequately demonstrated.

Contrary to the requirements of 21 CFR Part 211.192, your firm has not performed thorough investigations of specific failures or unexplained discrepancies and/or made a written record of its investigations, including the conclusions and follow-up. For example:

- At least five lots of Neurosyn Tablets failed dissolution testing and the cause was attributed to the use of the active ingredient [redacted] supplied by [redacted]. While at least one lot was reprocessed by regrinding, and recompressing, the investigation failed to include the follow-up regarding the other lots of the suspect [redacted].

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not followed in accordance with 21 CFR 211.113(b). Specifically,

- Not all personnel who enter the sterile core are monitored each day. Maintenance and cleaning personnel are only monitored during the annual gowning re-certification and/or semi-annual media fills. Additionally, not all operators who gown and enter the sterile core to assemble equipment or unload the autoclave are monitored.

Written procedures describing the handling of all written and oral complaints regarding a drug product were not followed in accordance with 21 CFR 211.198. Complaint records reviewed during this inspection were found to be deficient in that they do not routinely include:

- the findings of the investigation
- follow-up activities
- the lot number of the product involved
- reply to complainant.

You should know that these violations might result in FDA taking regulatory action without further notice to you. These actions include, but are not limited to, seizure and/or injunction.

Also, other federal agencies are informed about certain Warning Letters issued by FDA so they may consider this information when considering the award of contracts.

Our office is in receipt of the letter dated August 17, 2004 and signed by Dr. Shobha Varma addressing the steps you are taking to correct the deviations noted on the FDA 483 – Inspectional Observations issued at the close of the inspection on July 29, 2004. We have reviewed your summaries and current assumptions regarding your firm's previous validation activities for Oxytetracycline HCl bolus. A complete and comprehensive process validation study has not been performed. For example, your firm's validation summary for the revised validation protocol and addendum reports that "all samples for blend uniformity had low RSDs [redacted] showing homogeneous blend." However, the validation protocol specification for the blend uniformity is the average blend potency. The reported average blend potency for the last three validation lots failed the potency specification. Another example, the validation summary states all validation runs were mixed at [redacted] but the summary set a mixing speed range of [redacted]. Additionally, your firm's response lacks corrective and preventative actions for all cited cGMP deviations. As such, your response does not provide assurance to our office that you have identified the underlying issues for your failures or implemented full control over your Quality System.

Please submit, in writing, within fifteen working days of receiving this letter, your responses to the deviations identified in this letter. Your letter should include a description of the status of the corrective actions outlined in your firm's August 17, 2004 letter. Your reply should be sent to Nadine Nanko Johnson, Compliance Officer, at the above address.

Sincerely,

for Charles W. Sedgwick
District Director
Kansas City District

cc: Shobha Varma, Ph.D.
Director, Quality & Compliance
Boehringer Ingelheim Vetmedica, Inc.
2621 N. Belt Highway
St. Joseph, MO 64506